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PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

Module 6: Overview – Opioid Dependence Treatment with Buprenorphine/Naloxone

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History of Medical Practice for Opioid Addiction in the U.S.

- Physicians had been liberal prescribers of morphine in late 1800s/early 1900s, leading to rising rates of addiction.
- Harrison Act of 1914 prohibited physicians from prescribing narcotics to addicts, with criminal prosecution for violations.
- This legislation drove down morphine prescribing, even for severe pain cases.

History of Medical Practice for Opioid Addiction in the U.S.

- Opioids continued to be sold by criminal elements in the United States. Addiction, including imported heroin, continued to be a large problem.
- Methadone clinics to treat opioid addiction were established in 1974 and highly regulated at the federal level.
- Ongoing need for access to care for opioid addiction led to DATA 2000.

U.S. Legislation Enabling Office-Based Treatment of Opioid Dependence

- Drug Addiction Treatment Act of 2000 (DATA 2000): "Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment" (H.R. 4365, Children's Health Act of 2000)

Amended Controlled Substances Act: DATA 2000

- Revision in legislation now allows a physician to prescribe narcotic drugs in schedules III, IV, V, or combinations of such drugs, for the treatment of opioid dependence
- However:
  - Drugs and practitioners must meet certain requirements

Amended Controlled Substances Act: DATA 2000

- Narcotic drug requirements:
  - Drug must be approved by the US FDA for use in maintenance or detoxification treatment of opioid dependence
  - Must be in Schedule III, IV, or V
- Applies to opioids or combination of opioids and other controlled drugs

Amended Controlled Substances Act: DATA 2000

- Practitioners requirements:
  - Must be licensed “Qualifying physician” meeting one or more of these criteria:
  - Holds a subspecialty board certification in Addiction Psychiatry (ABPN) or ASAM certification or American Osteopathic Association certification
  - Has completed 8 hours of buprenorphine training provided by ASAM, AAAP, AMA, AOA, APA (or other organizations which may be designated by Department of HHS)
  - Has been an Investigator on clinical trial(s) for approval of Schedule III, IV, or IV narcotic opioid for detox./maintenance
  - Has other training deemed adequate by State medical licensing board or Secretary of HHS
  - Must affirm capacity to refer patients for appropriate counseling and ancillary services needed to treat opioid addiction

Amended Controlled Substances Act: DATA 2000

- Practitioner requirements:
  - Must register with SAMHSA and DEA.
  - No more than 30 patients in Year 1. Now can increase to 100 patients per practitioner after Year 1 of having waiver, but those who undertake the higher patient number must notify CSAT of their intent to do so by completing a second waiver.
  - Group practices: each waivered physician can have up to 100 patients after 1 year.

Amended Controlled Substances Act

- Practitioner requirements:
  - "Qualifying physician"
  - Waiver application requires physicians to endorse that they have the capacity to refer patients for appropriate counseling and ancillary services. Psychosocial interventions *in addition to* medication treatment are standard of care for treatment of severe opioid use disorders.
- State legislation:
  - A state may not preclude a practitioner from dispensing or prescribing buprenorphine for opioid dependence treatment unless the state enacts a law prohibiting the practitioner from doing so.

Opioid Treatment Programs

- 2013: Change in regulations now allows opioid treatment programs (OTPs, methadone maintenance programs) to dispense buprenorphine in same manner as office-based practitioners
- (Previously, OTPs had to dispense buprenorphine as they did for methadone with restricted take-home doses)
- OTPs can provide structure to patients who need closer observation than an office-based practitioner can provide; counseling is available; and some provide medical as well as mental health services

Amended Controlled Substances Act: DATA 2000

- Mandatory evaluation period:
  - During the first three years of buprenorphine approval, DHHS and DEA evaluated efficacy and safety
  - Safety included protection of the public health against diversion of the drug

Amended Controlled Substances Act: DATA 2000

- DHHS has evaluated:
  - Whether the treatment is effective in the office setting
  - Whether access to treatment has been increased
  - Whether there have been adverse consequences for the public health
- DEA has evaluated:
  - Extent of violations of the 30/100 patient limit
  - Extent of diversion of the medication
  - Physician record keeping and security measures related to on-site medication storage

Amended Controlled Substances Act: DATA 2000

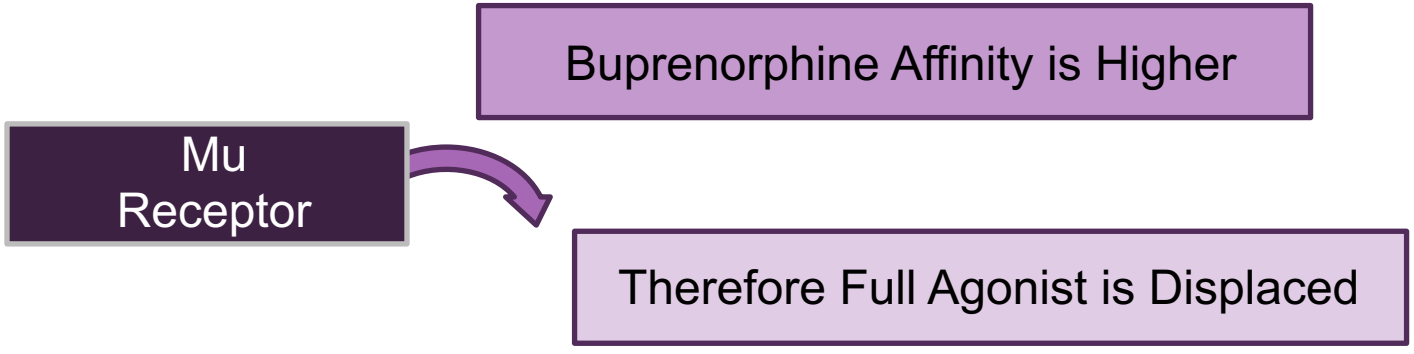
- Evaluation period:
  - On the basis of these evaluations, DHHS and DEA decided the law should remain in effect
  - Office-based treatment of opioid dependence continues as a treatment option for patients who need it
  - It is expected that number of providers offering this treatment will continue to grow as the treatment modality becomes more familiar to clinicians and patients

Buprenorphine

- Opioid partial agonist
- Schedule III (vs. methadone: Schedule II)
- Treatment modalities for buprenorphine:
  - Office-based treatment
    - Primary Care
    - Specialty (e.g.: Infectious Disease, GI, Psychiatry)
    - Substance abuse treatment clinics
  - Methadone maintenance programs

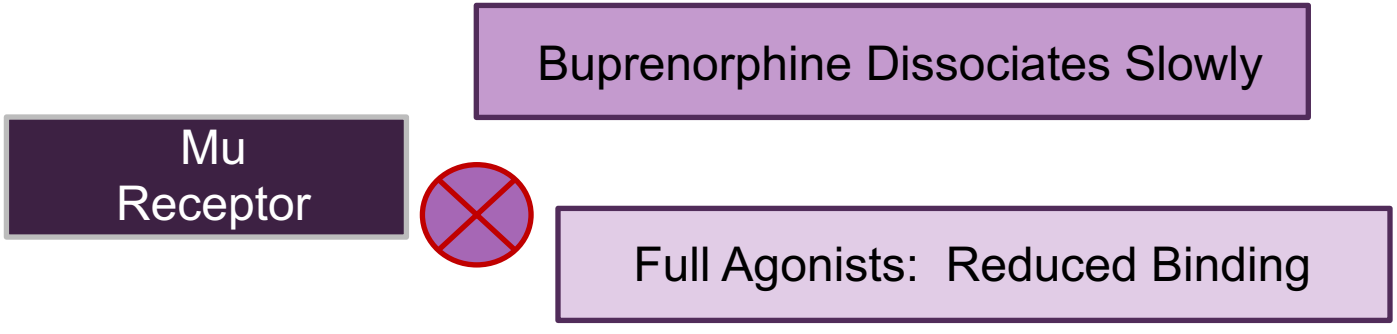
How Does Buprenorphine Work?

- AFFINITY is the strength with which a drug physically binds to a receptor
  - Buprenorphine has strong affinity; will displace full mu receptor agonists like heroin and methadone
  - Receptor binding strength (strong or weak), is NOT the same as receptor activation



How Does Buprenorphine Work?

- DISSOCIATION is the speed (slow or fast) of disengagement or uncoupling of a drug from the receptor
  - Buprenorphine dissociates slowly

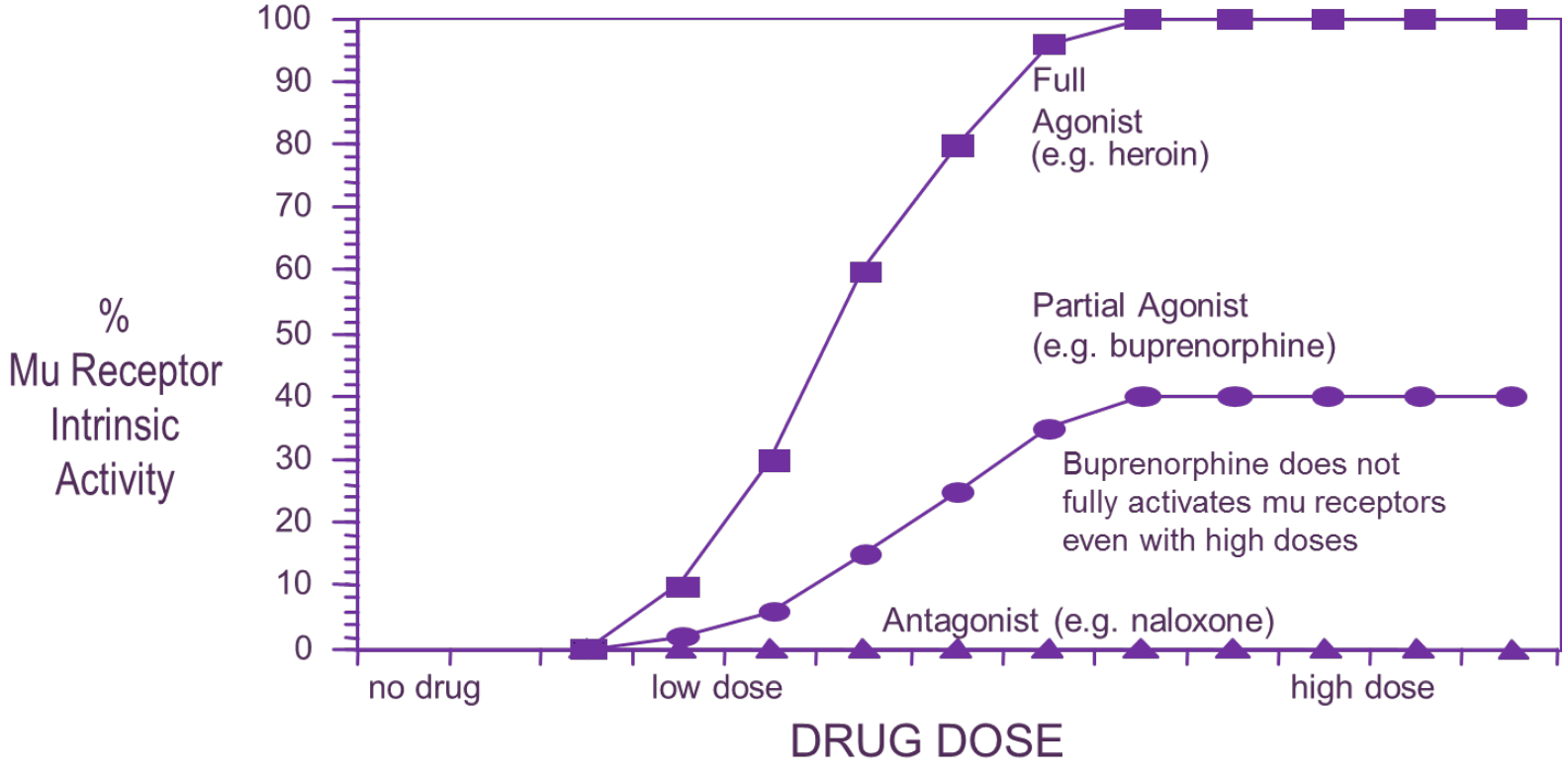


  - Therefore buprenorphine stays on the receptor a long time and blocks heroin, methadone and other opioids from binding to those receptors

How Does Buprenorphine Work?

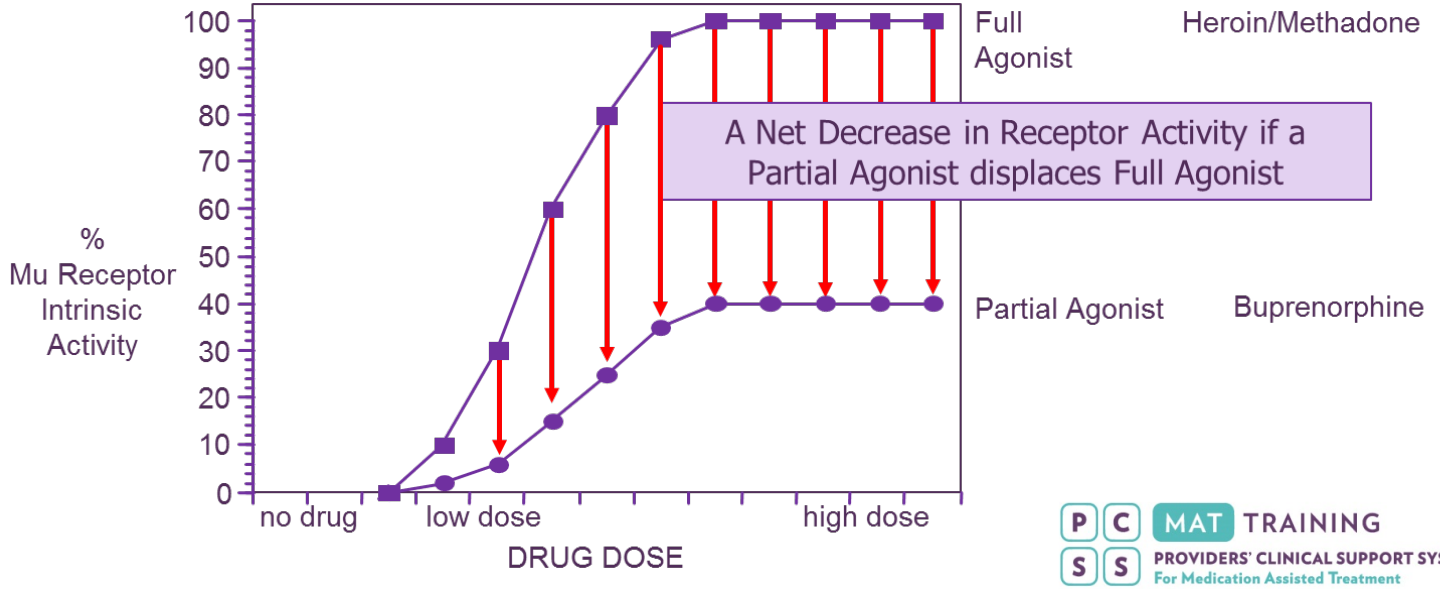
- Buprenorphine may reduce the effects of other opioids taken due to its high affinity for, and slow dissociation from, the mu receptor.
- However, buprenorphine is unlikely to block *all* effects from an opioid taken after initiation of buprenorphine treatment.
- This is because the availability of mu receptors is a dynamic process; while effects may be less, they are not likely to be completely eliminated.

Buprenorphine is a Partial Agonist



Pharmacology of Full vs. Partial Agonists

- Buprenorphine can precipitate withdrawal if it displaces a full agonist from the mu receptors
- Buprenorphine only partially activates the receptors; therefore, a net decrease in activation occurs and withdrawal develops



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Formulations of Buprenorphine

- Parenteral form for treatment of moderate to severe pain (not approved for opioid dependence treatment)
- 7-day Transdermal Patch (5, 10, and 20 µg/hour) for severe pain
- Sublingual forms (tablets and films) for treatment of opioid addiction; not approved for pain management
- Implant now in clinical trials for treatment of opioid addiction

Formulations of Buprenorphine

- Sublingual film or tablets for treatment of opioid dependence
  - Combination of buprenorphine/naloxone (Bup/Nx) is preferred drug for opioid addiction
  - Film Strengths:
    - Bup 2mg/Nx 0.5mg, Bup 4 mg/Nx 1 mg, Bup 8mg/Nx 2mg, Bup 12 mg/Nx 3 mg
    - Tablets: 2/0.5 mg and 8/2 mg
    - Dose Range: 4/1-24/6 mg daily; most stabilize on 12/3-16/4 mg daily
    - Combination developed to decrease diversion to injected abuse
    - Precipitated withdrawal if injected by opioid-dependent person

Clinical Forms of Buprenorphine

- There is also a sublingual tablet that is available as buprenorphine alone (without naloxone:
  - Bup 2mg or Bup 8 mg
  - For use in pregnancy
  - Available only as a generic
  - Has more diversion potential than the bup/nx combination; hence, the combination is the recommended form for treatment of opioid addiction except in pregnant, opioid dependent, women

Clinical Forms of Buprenorphine

- Buprenorphine/naloxone film (FDA approved 8/31/10)
  - Equivalent in strength to tablets
  - Dissolves more rapidly (5-6 min) than tablets
  - Participants in clinical trials preferred taste over that of tablets
  - Childproof foil packet improves safety of product
- Buprenorphine/naloxone tablets are now available as generic medications

Buprenorphine Formulation

- Buprenorphine/naloxone combination is recommended formulation for treatment of opioid dependence
- Naloxone is present to reduce diversion to injected abuse
- Naloxone plays no role in the patient's medication treatment:
  - Active by parenteral route
  - Not well absorbed by GI route

Public Health Issues with Buprenorphine

- Diversion: selling or giving a medication prescribed to an individual for a specific purpose to another person who misuses/abuses the medication; diversion is illegal
- Significant dangers for diversion of buprenorphine.
  - Abuse of the drug (known to occur widely in countries mainly using the buprenorphine-only formulation)
  - Buprenorphine/nx is being increasingly diverted in the U.S. Smaller doses minimize risk of precipitated withdrawal when injected.

Public Health Issues with Buprenorphine

- Adverse events related to buprenorphine abuse including overdoses/deaths:
- Lack of tolerance to opioids
- Drug-drug interactions since use of other drugs (licit and illicit) and/or alcohol occur frequently
- Important to understand the diversion/abuse potential of buprenorphine and not to give larger doses than patients need to treat their opioid addiction
- Favorable safety profile: (1) Ceiling effect of partial agonist protects against overdose when buprenorphine is taken on its own; (2) Lower risk (vs. methadone) of arrhythmias (long QT, Torsades de Pointes)
- Minimal subjective effects when used sublingually: clear-headed, improved energy/sleep

Diversion and Misuse

- Four possible groups that might attempt to divert and abuse buprenorphine/naloxone parenterally:
  - Persons physically dependent on illicit opioids
  - Persons on prescribed opioids (e.g., methadone), with this history concealed from bup/nx prescriber
  - Persons maintained on buprenorphine/ naloxone at higher-than-needed doses
  - Persons abusing, but not physically dependent on, opioids
  - Drug dealers with intent to sell buprenorphine/naloxone

Diversion and Parenteral Misuse

- Persons physically dependent on short-acting opioids like heroin or pain meds (prescribed or illicit):
  - If have short-acting full agonist on receptors:
    - Then injection of buprenorphine/naloxone will precipitate opioid withdrawal syndrome
  - If no short-acting full agonist on receptors:
    - By definition will already be experiencing some level of opioid withdrawal syndrome
    - Then injection of buprenorphine/naloxone will provide withdrawal relief and give agonist effects

Diversion and Parenteral Misuse

- Persons physically dependent on long-acting opioids like methadone (prescribed or illicit):
  - If have long-acting full agonist on receptors:
    - Then injection of buprenorphine/naloxone will precipitate opioid withdrawal syndrome
    - Methadone occupies receptors for days (T1/2 = up to 36 hrs). Cannot confirm absence of methadone and thus readiness for buprenorphine/naloxone without negative urine toxicology and/or naloxone challenge.
    - Injection carries risk of talc granulomatosis and necrosis

Diversion and Parenteral Misuse

- Persons physically dependent on sublingual buprenorphine/naloxone (prescribed or illicit):
  - If have long-acting buprenorphine/naloxone on receptors:
    - Then injection of buprenorphine/naloxone will not cause withdrawal, but instead give agonist effects
  - If no long acting buprenorphine/naloxone on receptors
    - Then injection of buprenorphine/ naloxone will provide agonist effects
  - Note that this population may dissolve and inject buprenorphine/ naloxone film, since they will have a ready supply if in maintenance treatment
  - Intranasal and rectal routes of abuse are also possible

Diversion and Parenteral Misuse

- Persons abusing, but not physically dependent on, opioids:
  - Then injection of buprenorphine/naloxone will give agonist effect because the low dose of naloxone will not completely block the buprenorphine.

Diversion and Sublingual Misuse

- Sublingual abuse may be less likely because agonist effect onset is slower and magnitude of effect is lower
- Two groups that might use by the sublingual route include:
  - Persons who are physically dependent on full agonist opioids
    - Periodic use to control full agonist opioid withdrawal syndrome is most likely pattern
  - Persons who are NOT physically dependent on any type of opioids
    - Experimental abuse for agonist effect is more likely in this group

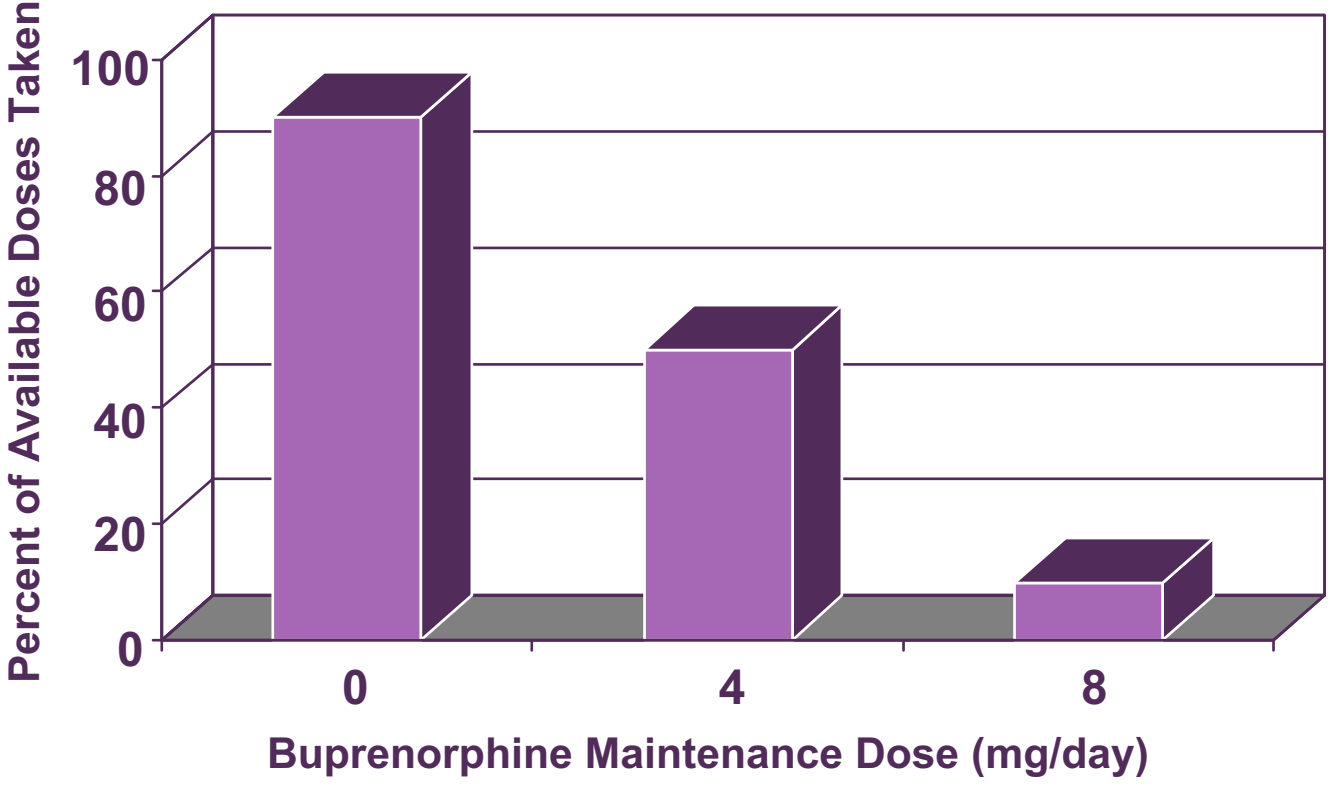
Buprenorphine Treatment

- Maintenance
- Medical Withdrawal

Buprenorphine Maintenance

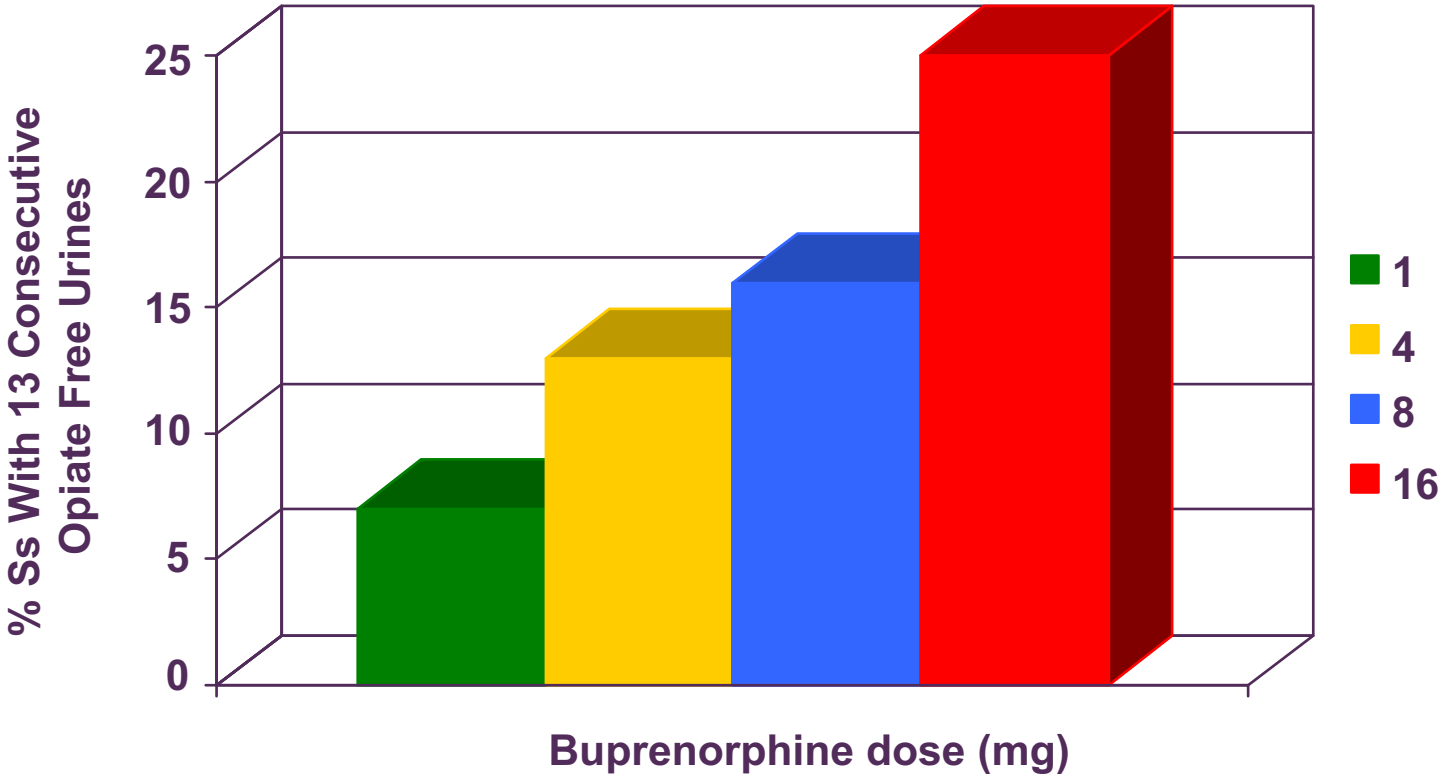
- Numerous outpatient clinical trials in people with opioid dependence compared efficacy with:
  - Methadone
  - LAAM
  - Placebo
- These trials reliably demonstrated that, in preventing relapse to heroin:
  - Buprenorphine is more effective than placebo
  - Buprenorphine is equally effective as moderate doses of methadone (e.g.: < 60 mg per day) with respect to treatment retention (59% at 6 months; Stein et al. 2005)
  - At higher methadone doses (> 60 mg/day), treatment retention increases to 80% (Hser et al., 2014)

Heroin Self-Administration During Buprenorphine Maintenance Declines with Buprenorphine Dose



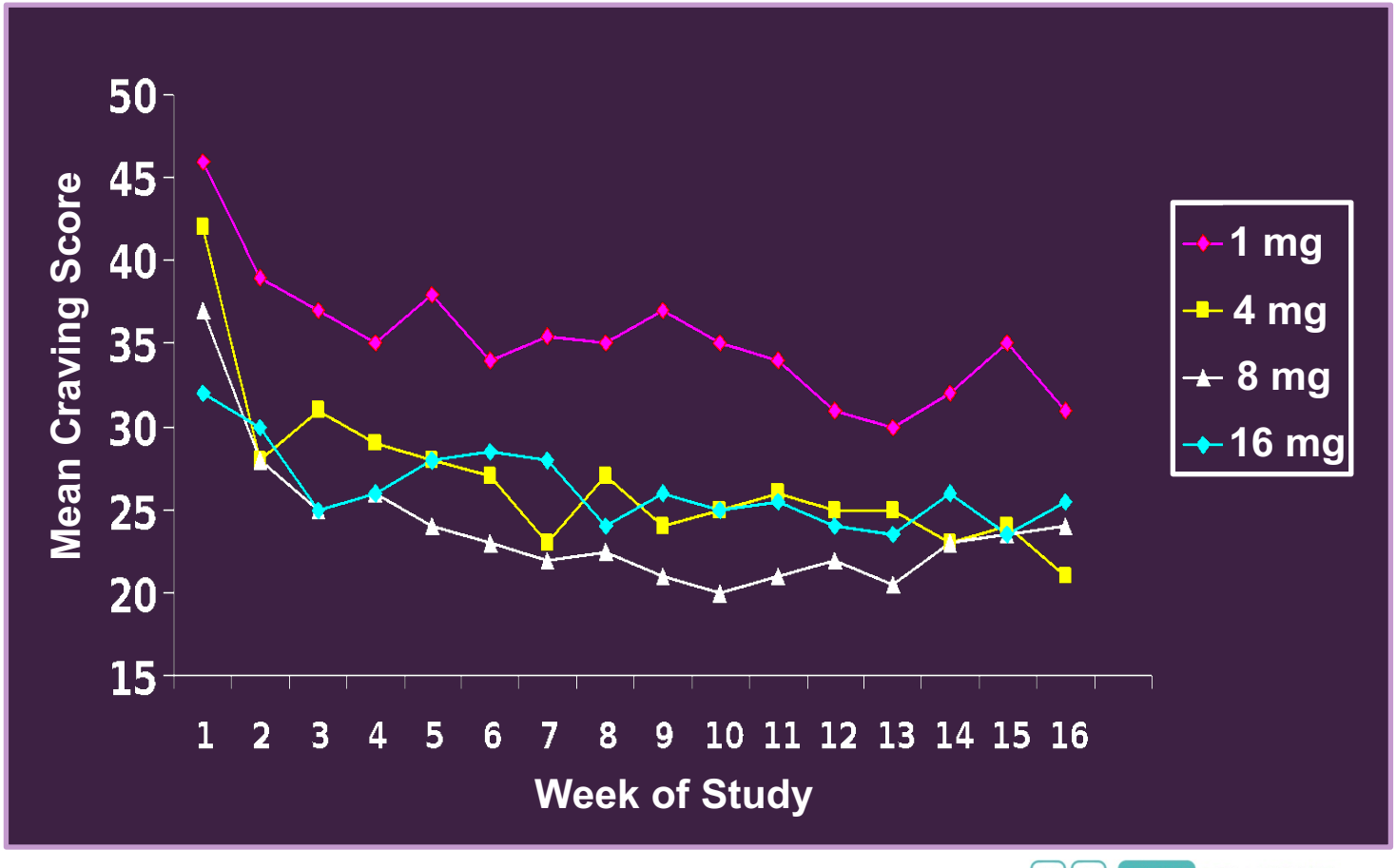
(Mello and Mendelson., 1980, Mello et al., 1982)

Different Doses of Buprenorphine: Opiate Use Decreases with Increased Dose of Buprenorphine



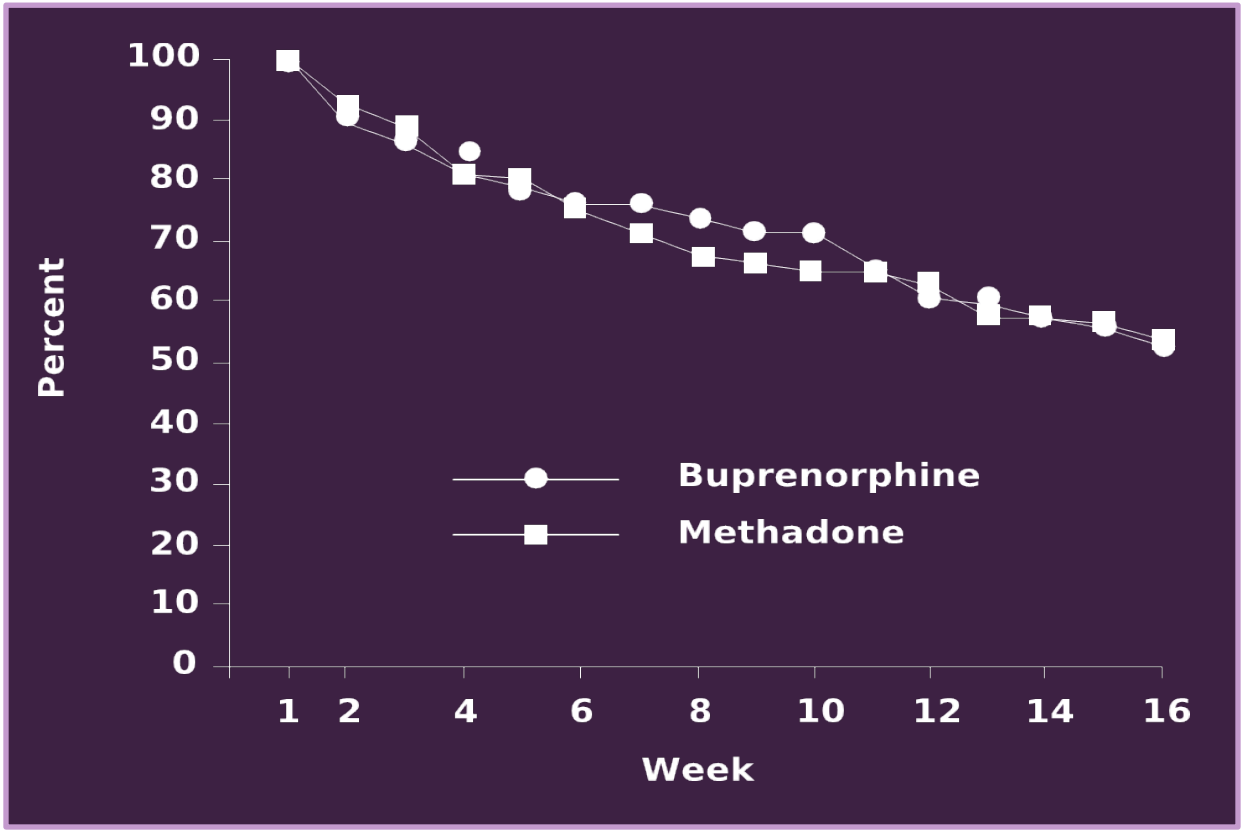
(Ling et al., 1998)

Mean Heroin Craving: 16 Week Completers: Reduced Craving with Therapeutic Buprenorphine Doses



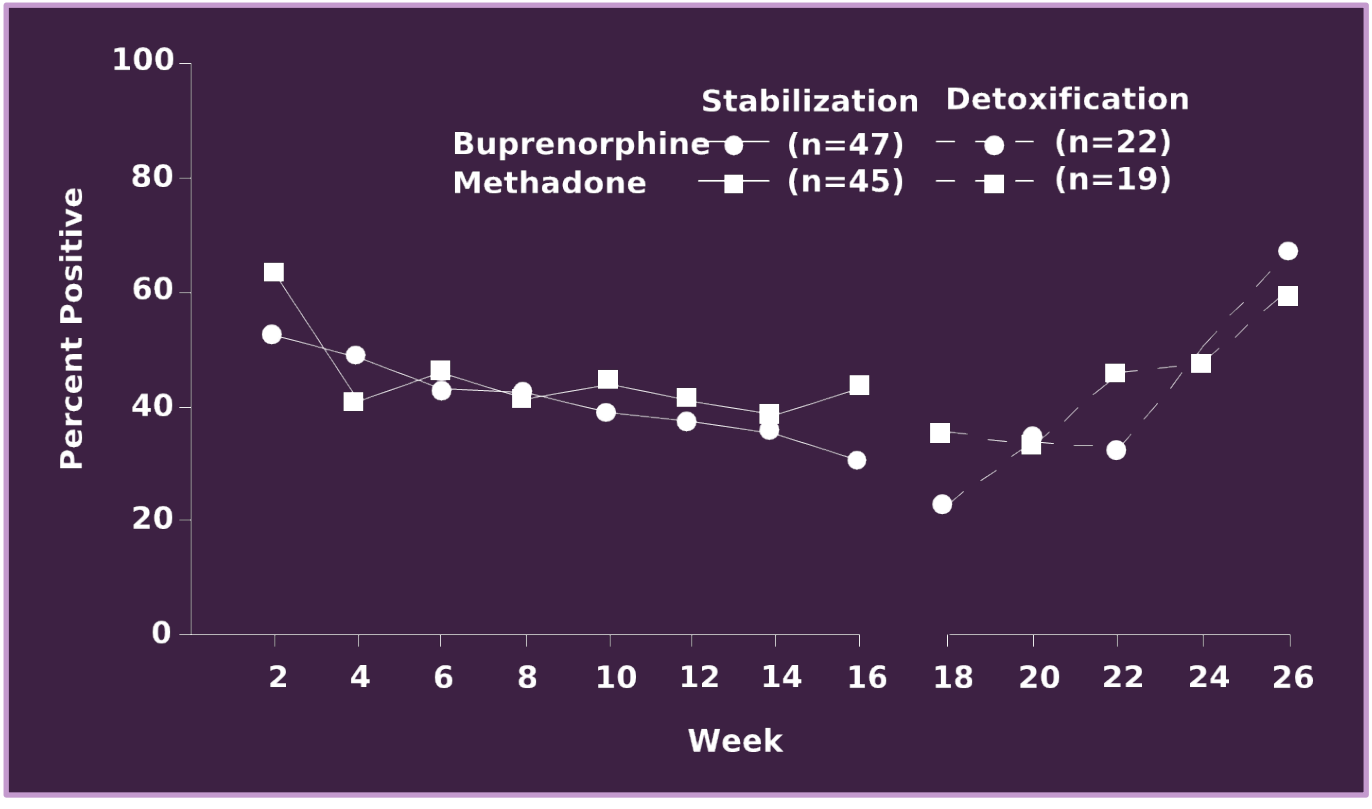
(Ling et al., 1998)

Buprenorphine – Methadone: Treatment Retention is Equivalent for the Two Medications



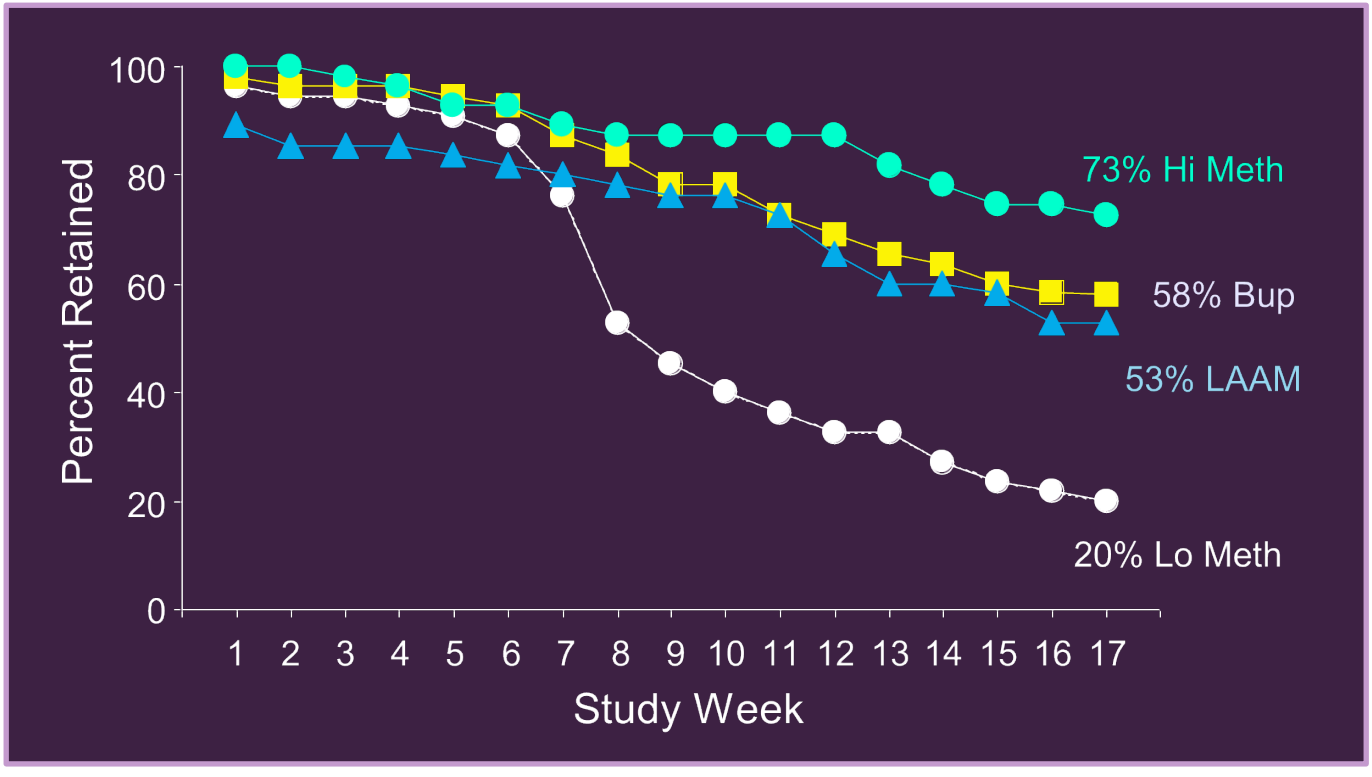
(Strain et al., 1998)

Buprenorphine – Methadone: Opioid Urine Results are Similar: Fewer Opioid Positive Urine with Treatment



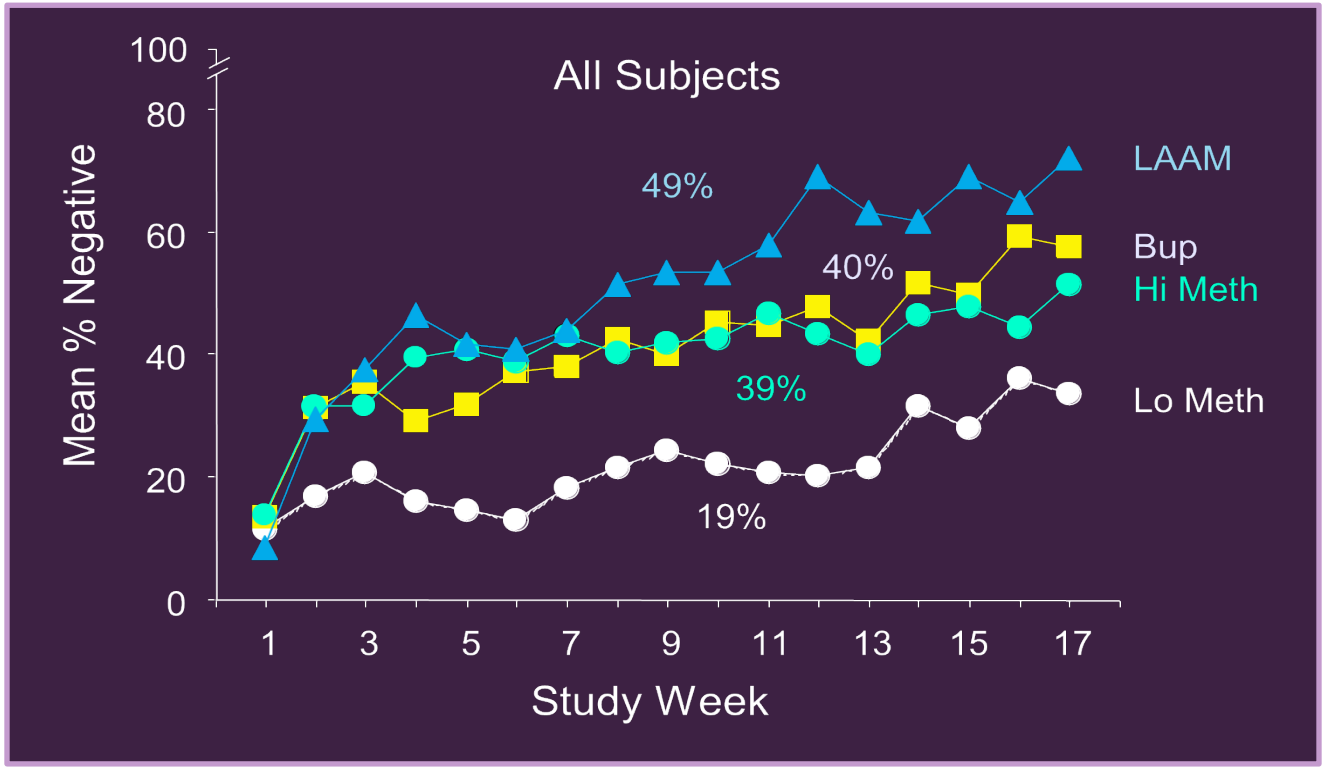
(Strain et al., 1998)

Buprenorphine, Higher Dose Methadone, LAAM: Treatment Retention Similar



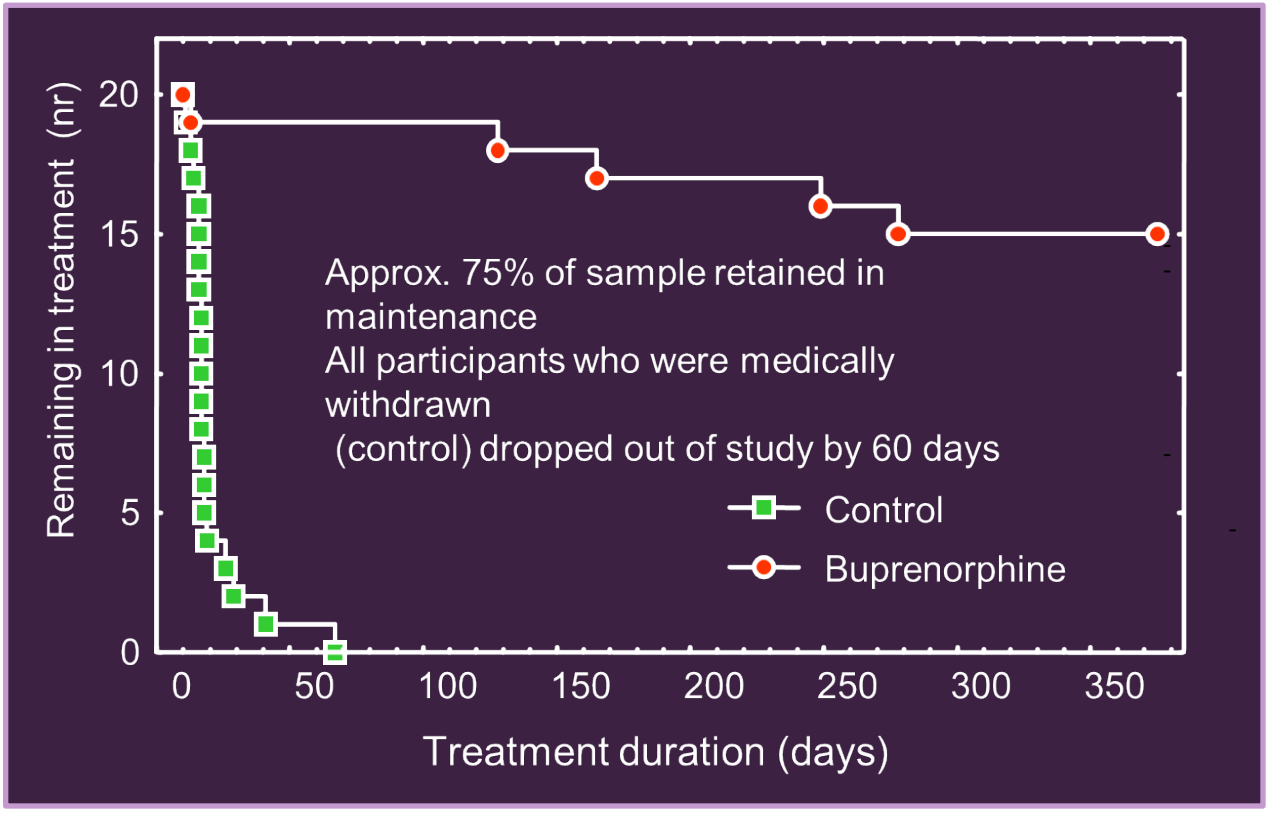
(Johnson et al., 2000)

Buprenorphine, Methadone, LAAM: More Opioid Negative Urines with Therapeutic Doses of Opioid in Maintenance Therapy



(Johnson et al., 2000)

Buprenorphine Maintenance/Withdrawal: Retention



(Kakko et al., 2003)

Buprenorphine Dosing

- Sublingual administration
- Film dissolves in 5-6 minutes; tablets can take up to approx. 10 minutes
- Taste is generally well tolerated
- Monitor dissolution with first doses
- Two films or tablets at one time is the recommended limit, as absorption is better and faster with a moist mouth
- Avoid acidic drinks like coffee or fruit juice

Buprenorphine: Side Effects

- Nausea/vomiting (consider precipitated withdrawal)
- Constipation
- Sedation (use of other sedating drugs or in those not currently dependent, but eligible for buprenorphine treatment by history)
- Transient elevations in liver transaminases possible (Hep C at higher risk)

Buprenorphine – Methadone Comparison

	Buprenorphine	Methadone
Regulation/ Diversion	Partial agonist May be diverted Less regulation Can be used in office-based treatment of opioid dependence	Full agonist May be diverted Toxicity risk greater Specialized centers required for treatment of opioid dependence
Dose/side Effects	Preferred is combo: bup/nlx Fewer side effects Precipitated withdrawal potential Reduced risk of overdose	Relatively high dose required for tolerance induction; continued opiate effects, sedation
Ease of Use	Induction generally requires clinical monitoring Available by prescription Withdrawal better tolerated Favorable side effect profile	Induction and dosing straightforward first doses should be monitored Withdrawal challenging; Complaints of significant discomfort Risk of ventricular arrhythmias
Drug Interactions	No clinically significant with HIV meds except atazanavir; rifampin assoc. with withdrawal; BZD (particularly injected) and CNS depressants a concern	Numerous, especially HIV meds, TB meds, some anticonvulsants; concern about interactions with BZDs and other CNS depressants

Summary

- Buprenorphine
  - Opioid partial agonist: less opioid effects than heroin or methadone; less potential for toxicity
  - As effective as moderate doses of methadone in treatment of opioid addiction
  - Induction generally requires clinical monitoring
  - Buprenorphine administration will result in precipitated withdrawal in person physically dependent on opioids if administered following recent opioid use

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